Claims

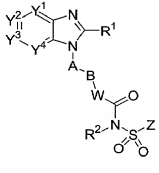
1. A method of treating rheumatoid arthritis in a mammal, said method comprising administering an agent that inhibits prostaglandin EP4 receptor (EP4) activity.

2. The method of claim 1, wherein said agent is administered in an amount sufficient to reduce interleukin (IL)-6 levels, reduce serum amyloid A (SAA) levels, reduce joint inflammation, reduce joint hyperplasia, reduce joint ankylosis, and/or increase joint mobility.

3. The method of claim 1, wherein said mammal is human.

4. The method of claim 1, wherein said agent is EP4 selective.

5. The method of claim 1, wherein said agent is an aryl or heteroaryl fused imidazole compound of the following Formula I



(I)

or the pharmaceutically acceptable salts thereof, wherein

Y^1, Y^2, Y^3 and Y^4 are independently selected from N, CH or C(L);

R^1 is H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-7} cycloalkyl, C_{1-8} alkoxy, halo-substituted C_{1-8} alkoxy, C_{1-8} alkyl-S(O)m-, Q^1-, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, amino, mono- or di-(C_{1-8} alkyl)amino, C_{1-4}alkyl-C(=O)-N(R^3)- or C_{1-4}alkyl-S(O)m-N(R^3)-, wherein said C_{1-8} alkyl, C_{2-8} alkenyl and C_{2-8} alkynyl are optionally substituted with halo, C_{1-3} alkyl, hydroxy, oxo, C_{1-4} alkoxy-, C_{1-4} alkyl-S(O)m-, C_{3-7} cycloalkyl-, cyano, indanyl, 1,2,3,4-tetrahydronaphtyl, 1,2-dihydronaphtyl, pyrrolidinyl, piperidyl, oxopyrrolidinyl, oxopiperidyl, Q^1-, Q^1-C(=O)-, Q^1-O-, Q^1-S(O)m-, Q^1-C_{1-4}alkyl-O-, Q^1-C_{1-4}alkyl-S(O)m-, Q^1-C_{1-4}alkyl-C(O)-N(R^3)-, Q^1-C_{1-4}alkyl-N(R^3)- or C_{1-4}alkyl-C(O)-N(R^3)-;

Q^1 is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 4 heteroatoms selected from O, N and S, and is optionally substituted with halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4}alkyl)amino, cyano, HO-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4}alkyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4}alkylC(=O)-, HO(O=)C-, C_{1-4}alkyl-O(O=)C-, R^3N(R^4)C(=O)-, C_{1-4} alkylsulfonylamino, C_{3-7} cycloalkyl, R^3C(=O)N(R^4)- or NH_2(HN=)C-;

A is a 5-6 membered monocyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-6 membered monocyclic aromatic ring is optionally substituted with up to 3 substituents selected from halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4}alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, cyano, HO-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4}alkyl, C_{1-4} alkylsulfonyl,

aminosulfonyl, acetyl, $R^3N(R^4)C(=O)$-, HO(O=)C-, C_{1-4}alkyl-O(O=)C-, C_{1-4} alkylsulfonylamino, C_{3-7} cycloalkyl, $R^3C(=O)N(R^4)$- and $NH_2(HN=)C$-;

B is halo-substituted C_{1-6} alkylene, C_{3-7} cycloalkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, -O-C_{1-5} alkylene, C_{1-2} alkylene-O-C_{1-2} alkylene or C_{1-6} alkylene optionally substituted with an oxo group or C_{1-3} alkyl;

W is NH, N-C_{1-4} alkyl, O, S, N-OR^5 or a covalent bond ;

R^2 is H, C_{1-4} alkyl, OH or C_{1-4} alkoxy;

Z is a 5-12 membered monocyclic or bicyclic aromatic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, cyano, HO-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4}alkyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4}alkylC(=O)-, $R^3C(=O)N(R^4)$-, HO(O=)C-, C_{1-4}alkyl-O(O=)C-, C_{1-4} alkylsulfonylamino, C_{3-7} cycloalkyl, $NH_2(HN=)C$-, Q^2-S(O)m-, Q^2-O-, Q^2-N(R^3)- or Q^2- ;

L is halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, halo-substituted C_{1-4} alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, cyano, HO-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4}alkyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4}alkylC(=O)-, HO(O=)C-, C_{1-4}alkyl-O(O=)C-, C_{1-4} alkylsulfonylamino, C_{3-7} cycloalkyl, $R^3C(=O)N(R^4)$-, $NH_2(HN=)C$-, $R^3N(R^4)C(=O)$-, $R^3N(R^4)S(O)m$-, Q^2-, Q^2-C(=O)-, Q^2-O-, Q^2-C_{1-4}alkyl-O-, or two adjacent L groups are optionally joined together to form an alkylene chain

having 3 or 4 members in which one or two (non-adjacent) carbon atoms are optionally replaced by oxygen atoms;

m is 0, 1 or 2;

R^3 and R^4 are independently selected from H and C_{1-4} alkyl ;

R^5 is H, C_{1-4} alkyl, C_{1-4} alkyl-(O=)C- or C_{1-4} alkyl-O-(O=)C- ; and

Q^2 is a 5-12 membered monocyclic or bicyclic aromatic ring, or a 5-12 membered tricyclic ring optionally containing up to 3 heteroatoms selected from O, N and S, wherein said 5-12 membered monocyclic or bicyclic aromatic ring is optionally substituted with halo, C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, hydroxy, C_{1-4} alkoxy, halo-substituted $C1_{1-4}$ alkoxy, C_{1-4} alkylthio, nitro, amino, mono- or di-(C_{1-4} alkyl)amino, cyano, HO-C_{1-4} alkyl, C_{1-4} alkoxy-C_{1-4}alkyl, C_{1-4} alkylsulfonyl, aminosulfonyl, C_{1-4}alkyl-(O=)C-, $R^3(R^4)$C(=O)N-, HO(O=)C-, C_{1-4} alkyl-O(O=)C-, C_{1-4} alkylsulfonylamino, C_{3-7} cycloalkyl, C_{1-4} alkyl-C(=O)NH- or NH_2(HN=)C-.

6. A method of identifying an agent that selectively inhibits EP4 activity *in vivo*, said method comprising:

administering an agent to an animal model of rheumatoid arthritis, wherein said agent is identified as selectively inhibiting EP4 activity or selectively binding
EP4; and

measuring joint inflammation, joint swelling, joint ankylosis, interleukin (IL)-6, SAA protein, and/or joint mobility;

wherein said agent is identified as selectively inhibiting EP4 activity *in vivo* if said agent causes reduced joint inflammation, reduced joint swelling,

reduced joint ankylosis, reduced interleukin (IL)-6, reduced SAA protein, and/or increased joint mobility in said animal.